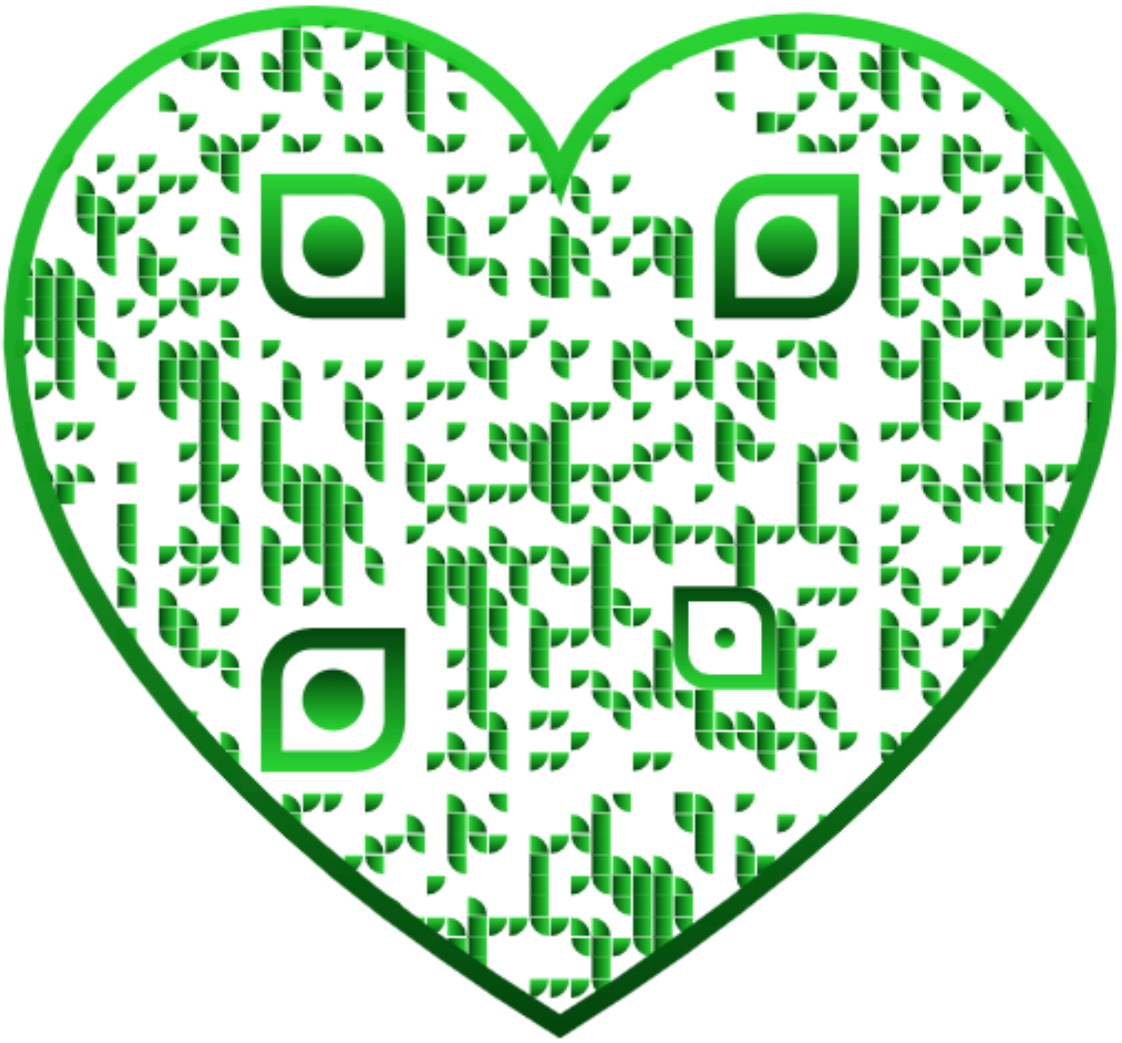
7. Radiopharmaceuticals



Introduction

- A radiopharmaceutical is a radioactive compound used for the diagnosis and therapeutic treatment of human diseases.
- Nearly 95% of radiopharmaceuticals are used for diagnostic purposes,
- Radiation is an inherent characteristic of all radiopharmaceuticals,
  - Patients always receive an unavoidable radiation dose

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- In the case of therapeutic radiopharmaceuticals, radiation is that produces the therapeutic effect.

- A radiopharmaceutical can be:

  1) as simple as a radioactive element such as **^{133}Xe**,

  2) a simple salt such as **^{131}I-NaI**, or

  3) a labeled compound such as **^{131}I-iodinated proteins** and **^{99m}Tc-labeled compounds**.

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- A radiopharmaceutical has two components
  - **Radionuclide**
    - Provides the desired radiation characteristics
  - **Pharmaceutical**
    - A chemical compound that determine the *in vivo* distribution & physiological behavior of the radionuclide
    - Other additives

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- A suitable radionuclide is ***tagged*** onto the chosen pharmaceutical,
  - After administration of the radiopharmaceutical, radiations emitted from it are detected by a radiation detector.
  - Thus, the morphologic structure or the physiologic function of the organ can be assessed.

Radionuclide

- Radionuclides are ***unstable*** nuclei that are stabilized upon radioactive decay.

- Approximately **3000 nuclides** have been discovered so far,
  - Most of these are unstable,
  - Only about 30 of these are routinely used in nuclear medicine.

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- The nucleus of an atom is composed of ***protons*** and ***neutrons***, collectively called ***nucleons***.
- The number of protons in a nucleus is called the ***atomic number*** of the atom, denoted by Z.
- The number of neutrons is denoted by N.
- The total number of nucleons in a nucleus is referred to as the ***mass number***, denoted by A. Thus, A is equal to Z + N.

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- The ratio of the number of neutrons to the number of protons (N/Z) is an approximate ***index of the stability of a nuclide***.
- This ratio equals 1 in the stable nuclei with a low atomic number, such as $^{12}_{6}C$, $^{16}_{8}O$, and $^{14}_{7}N$,
- The ratio increases with the increasing atomic number of the nucleus.
  - For example, it is 1.40 for $^{127}_{53}I$ and 1.54 for $^{208}_{82}Pb$.

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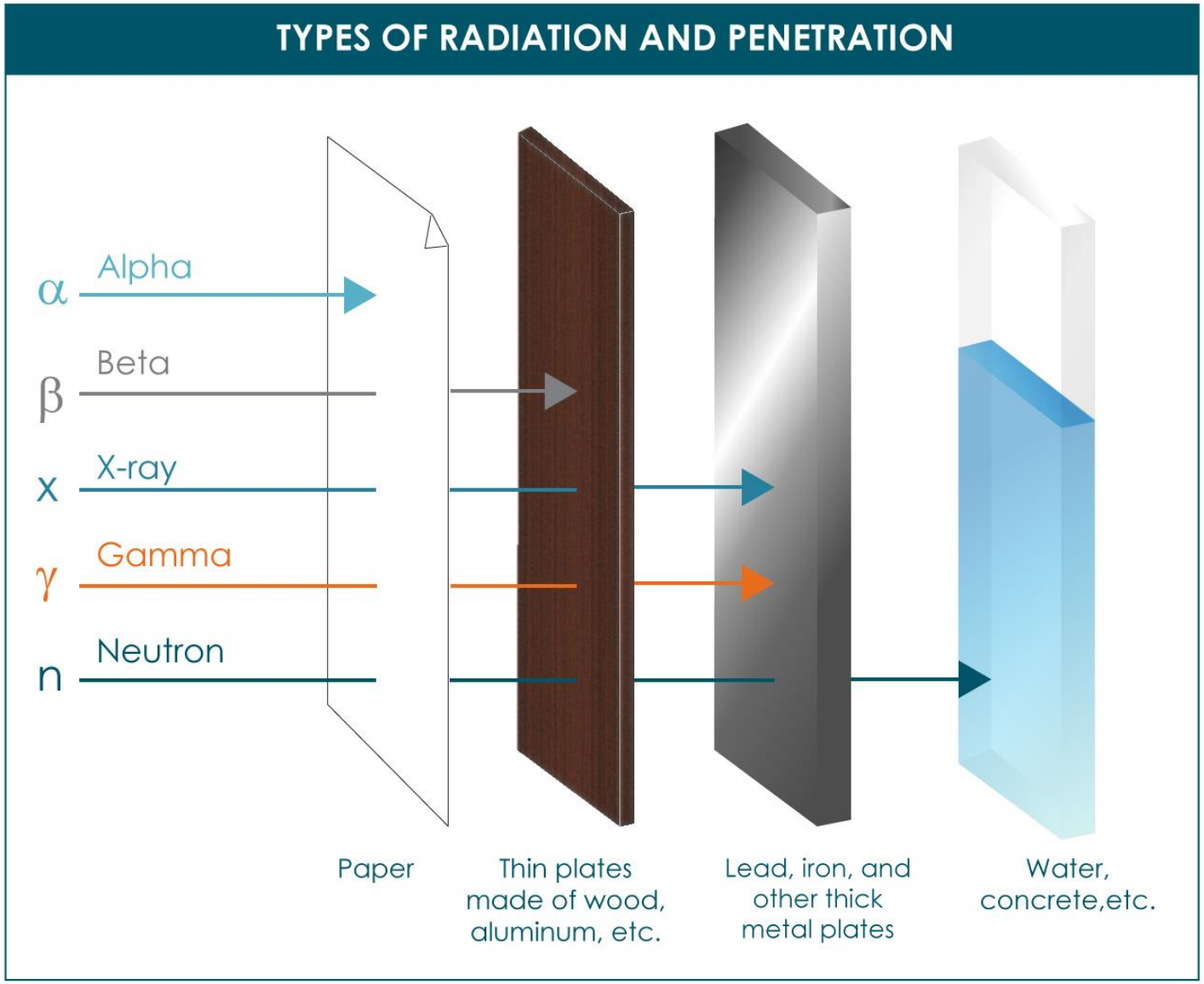
- Unstable nuclei decay by emitting different types of ionizing radiation:
  - Alpha (α) radiation
  - Negatron (β^-) radiation
  - Positron (β^+) radiation, and
  - Gamma (γ) radiation


TYPES OF RADIATION AND PENETRATION
α
Alpha
β
Beta
x
X-ray
γ
Gamma
n
Neutron
Paper
Thin plates made of wood, aluminum, etc.
Lead, iron, and other thick metal plates
Water, concrete,etc.

Decay of Radionuclide

- If the daughter nucleus is **stable**, the spontaneous transformation ends,
- If the daughter is **unstable**, the process continues until a stable nuclide is reached.

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- Depending on the radiation characteristics of the radionuclide, the radiopharmaceutical is used either for **diagnosis** or for **therapy**.
  - Gamma emission or positron (β^+) emission for Diagnostic applications.
  - If by particulate decay (alpha or beta) for therapeutic applications

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Alpha (α) decay

- Alpha (α) decay is characterized by the emission of an alpha particle from the nucleus.
- The ***α particle*** is a helium ion containing two protons and two neutrons.

$$ {}^{A}_{Z}X \rightarrow {}^{A-4}_{Z-2}Y + {}^{4}_{2}He^{+2} $$

$$ {}^{235}_{92}U \rightarrow {}^{231}_{90}Th + {}^{4}_{2}He^{2+} $$

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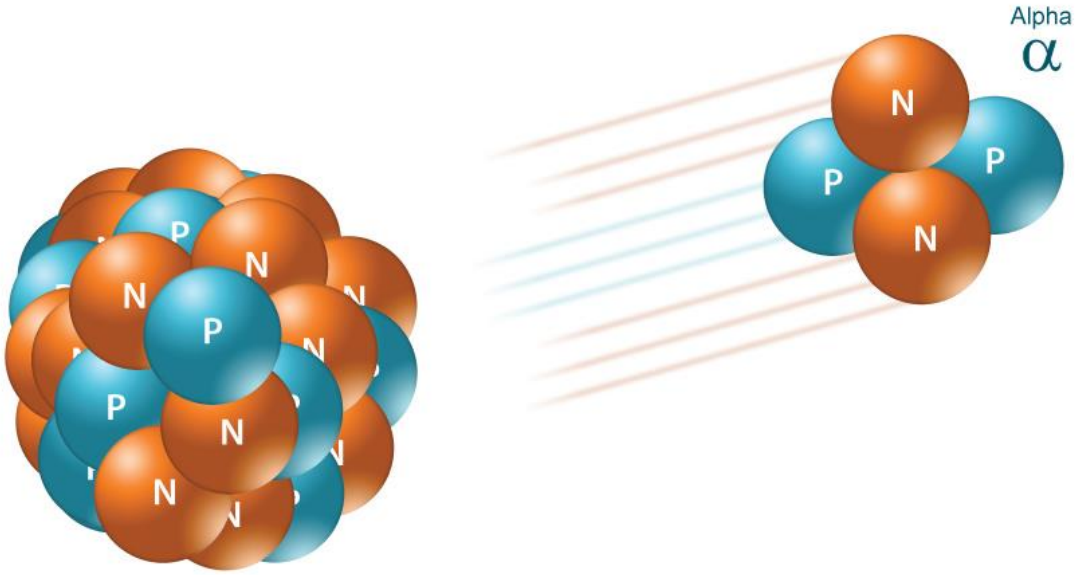
Alpha
α
N
P
P
N
P
N
N
P
N
N
N

...

- The α particles are mono-energetic,
  - Range in matter is ***very short*** (on the order of 10^{-6} cm) due to their mass,
  - Leave much of its energy on a very small area (only a few cell diameters).
  - Used only for ***therapeutic*** purposes.
  - Their clinical use is very limited, and they are mainly used for research purposes.

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Beta-Minus (Negatron) Decay

- Nuclei that are "neutron rich" or "proton deficient"
- In β^- decay, a neutron (n) essentially decays into a proton (p) and a β^- particle.

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- After β^- decay, the atomic number of the daughter nuclide is one more than that of the parent nuclide,
- The mass number remains the same for both nuclides

$$ {}^{A}_{Z}X \rightarrow {}^{A}_{Z+1}Y + \beta^- + \bar{\nu} $$

...

- The β^- particle is emitted with variable energy from zero up to the decay energy.
- The decay or transition energy is the difference in energy between the parent and daughter nuclides.
- An antineutrino carries away the difference between the β^- particle energy and the decay energy.

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$$^{131}_{53}\mathrm{I} \rightarrow {}^{131}_{54}\mathrm{Xe} + \beta^- + \overline{\nu}$$

$$^{59}_{26}\mathrm{Fe} \rightarrow {}^{59}_{27}\mathrm{Co} + \beta^- + \overline{\nu}$$

$$^{99}_{42}\mathrm{Mo} \rightarrow {}^{99\mathrm{m}}_{43}\mathrm{Tc} + \beta^- + \overline{\nu}$$

$$^{60}_{27}\mathrm{Co} \rightarrow {}^{60}_{28}\mathrm{Ni} + \beta^- + \overline{\nu}$$

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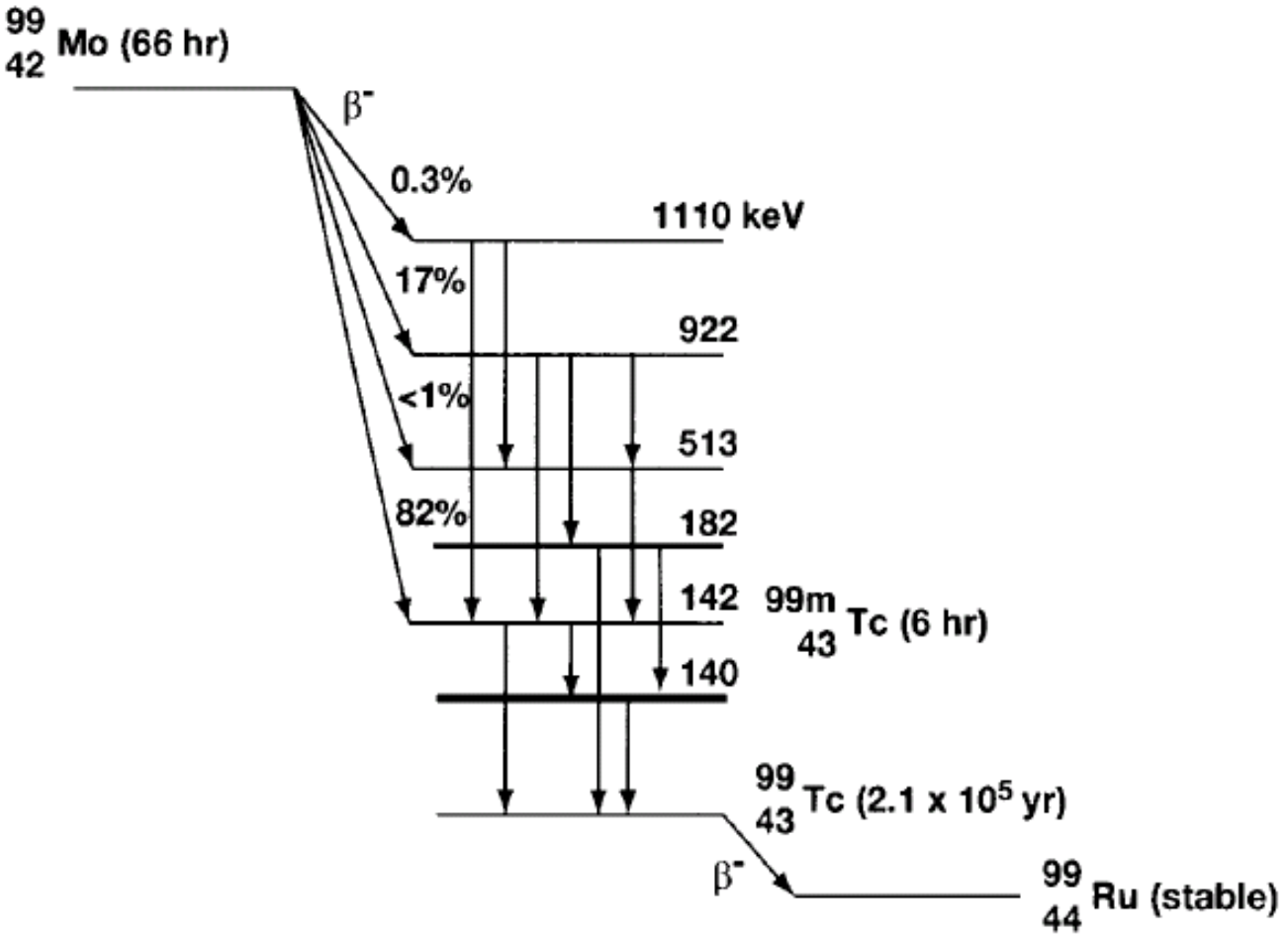
- Decay scheme of ^{99}Mo



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- Beta emitters represent different energy levels, and have different range in matter (40 – 100μm) depending on their energy.

- Beta emitting radionuclides are used in radiopharmaceuticals mainly for therapeutic purposes.

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Beta-plus – β^+ (Positron) Decay

- Nuclei that are "neutron deficient" or "proton rich"
  - i.e., have an N/Z ratio less than that of the stable nuclei
  - Decay by β^+ - particle emission accompanied by the emission of a *neutrino (V)*,

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- In β^+ decay, a proton transforms into a neutron by emitting a β^+ - particle
  - The daughter nuclide has an atomic number that is 1 less than that of the parent
- Since a β^+ particle can be emitted with energy between zero and decay energy, the neutrino carries away the difference between decay energy and β^+ energy.

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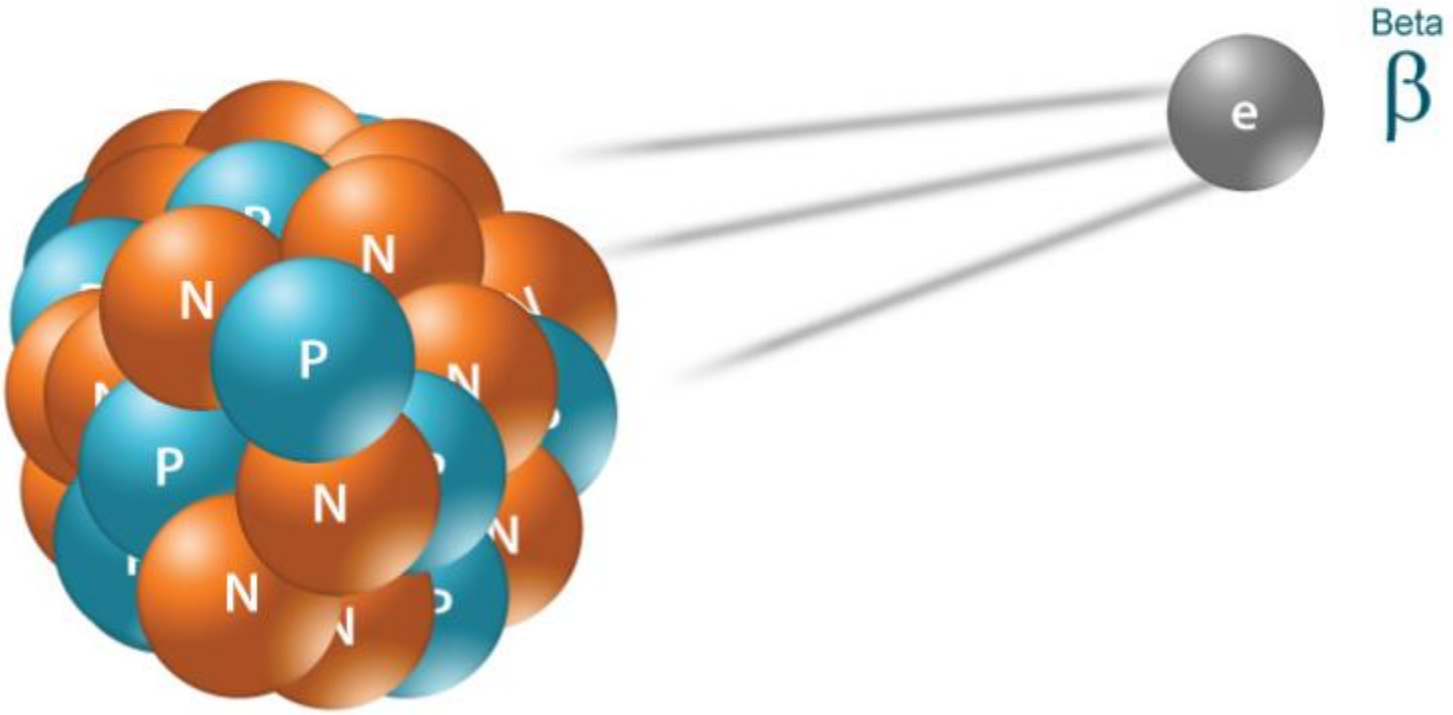
$$ {}^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + \beta^{+} + \nu $$

$$ {}^{15}_{8}O \rightarrow {}^{15}_{7}N + \beta^{+} + \nu $$


Beta
β
e
N
P
N
P
N
N
N

...

Gamma radiation

- A nucleus can remain in several excited energy states above the ground state.
- All these excited states are referred to as ***isomeric states*** and decay to the ground state.
- The decay of an upper excited state to a lower excited state is called the ***isomeric transition***.

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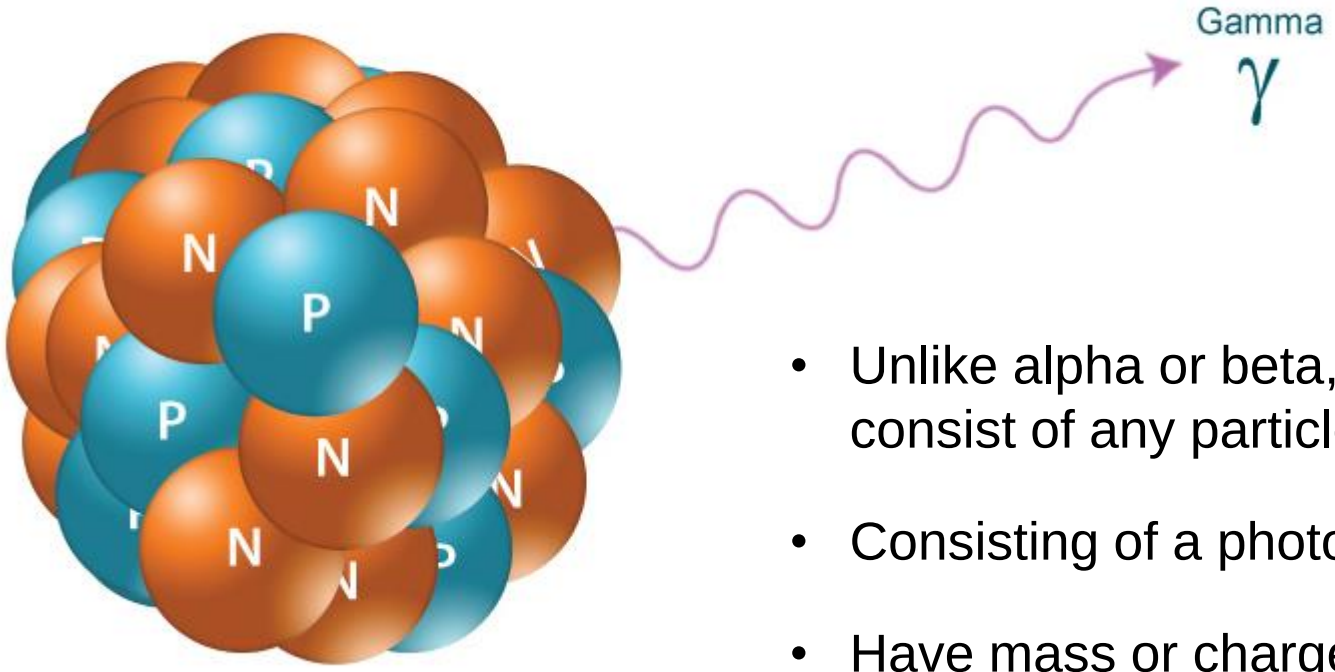
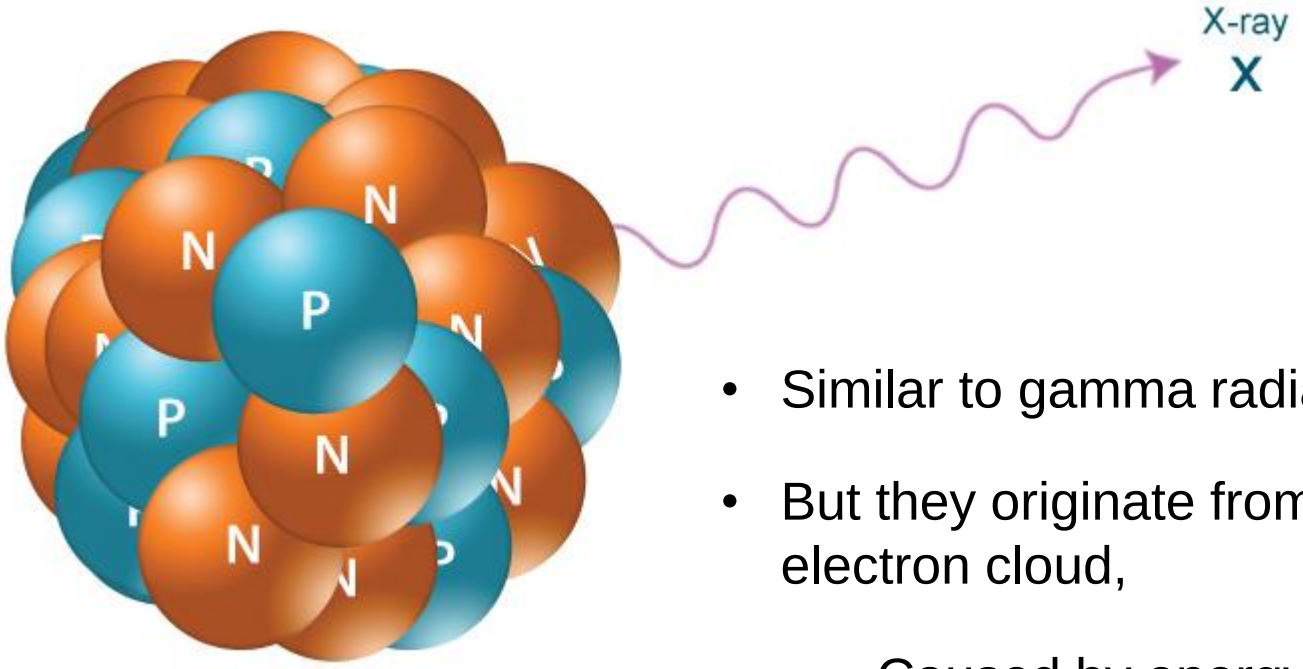
- In isomeric transition, the energy difference between the energy states may appear as ***gamma (γ) rays.***
- Gamma radiation is characterized as ***electromagnetic radiation***
- When used in ***diagnostic*** radiopharmaceuticals, gamma rays are powerful enough to be detected outside the body of the patient



- Unlike alpha or beta, does not consist of any particles,
- Consisting of a photon of energy
- Have mass or charge,
- Can travel much farther through air than alpha or beta, losing half its energy for every 500 feet.



- Similar to gamma radiation,
- But they originate from the electron cloud,
  - Caused by energy changes in an electron,
  - When moving from a higher energy level to a lower one,
- X-Rays are longer-wavelength and lower energy

Production of Radionuclide

- All radionuclides commonly administered to patients in nuclear medicine are artificially produced
- Most are produced by:
  1) Cyclotrons
  2) Nuclear reactors
  3) Radionuclide generators

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1) Cyclotron Reactors

- By bombarding stable nuclei (target elements) with high-energy charged **particles**
  - Such as ***protons, deuterons, and α particles***
- When targets of stable elements are irradiated nuclear reactions take place.

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- Examples

  - Iodine-123 can be produced by several nuclear reactions in cyclotron such as:
    - $^{121}Sb(\alpha, 2n)\ ^{123}I$
    - $^{123}Te\ (p, n)\ ^{123}I$
    - $^{122}Te\ (d, n)^{123}I$
    - $^{124}Te(p, 2n)\ ^{123}I$.

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- Gallium-67 can also be produced by several nuclear reactions
  - $^{66}Zn(d, n)^{\mathbf{67}}\mathbf{Ga}$,
  - $^{68}Zn(p, 2n)\ ^{67}Ga$,

...

2) Nuclear Reactors

- A nuclear reactor is constructed with fuel rods made of **fissile materials** such as enriched ^{235}U & ^{239}Pu
  - *Fission is defined as the breakup of a heavy nucleus into two fragments of approximately equal mass,*
    - *accompanied by the emission of two to three* ***neutrons*** *with mean energies of about 1.5 MeV.*

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- When a target element is inserted in the reactor core,
  - And, a thermal ***neutron*** will interact with the target nucleus to produce various radionuclides.
  - Two types of interaction with neutrons:
    1) Fission of heavy elements
    2) Neutron capture reaction

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Fission Reaction

- In the reactor core, heavy nuclei absorb thermal neutrons and undergo fission.
- Fissionable heavy elements are ^{235}U, ^{239}Pu, ^{237}Np, ^{232}Th.

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- Many clinically useful radionuclides such as ^{131}I, ^{99}Mo, ^{133}Xe, and ^{137}Cs are produced by fission of ^{235}U.

$$
\begin{aligned}
{}^{235}_{92}\mathrm{U} + {}^{1}_{0}\mathrm{n} \rightarrow {}^{236}_{92}\mathrm{U} &\rightarrow {}^{131}_{53}\mathrm{I} + {}^{102}_{39}\mathrm{Y} + 3\,{}^{1}_{0}\mathrm{n} \\
&\rightarrow {}^{99}_{42}\mathrm{Mo} + {}^{135}_{50}\mathrm{Sn} + 2\,{}^{1}_{0}\mathrm{n} \\
&\rightarrow {}^{117}_{46}\mathrm{Pd} + {}^{117}_{46}\mathrm{Pd} + 2\,{}^{1}_{0}\mathrm{n} \\
&\rightarrow {}^{133}_{54}\mathrm{Xe} + {}^{101}_{38}\mathrm{Sr} + 2\,{}^{1}_{0}\mathrm{n}
\end{aligned}
$$

...

- Nuclides produced by fission may range in atomic number from about 28 to nearly 65
- These isotopes of different elements are separated by appropriate chemical procedures that involve:
  - Precipitation
  - Solvent extraction
  - Ion exchange
  - Chromatography
- The fission products are usually neutron rich and decay by β^- particle emission

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Neutron Capture Reaction

- The target nucleus captures one thermal neutron and emits gamma (γ) rays to produce an ***isotope*** of the same element
- Some examples of neutron capture reactions are
  - $^{98}Mo(n, \gamma)$ **^{99}Mo**
  - $^{196}Hg(n, \gamma)$ **^{197}Hg**
  - $^{50}Cr\ (n, \gamma)$ **^{51}Cr**

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3) Radionuclide Generators

- Cyclotrons and Nuclear reactors are ***expensive***.
  - Very short-lived radionuclides are available only in the institutions that have the cyclotron or reactors,
  - They cannot be supplied to remote institutions or hospitals because they decay rapidly,
  - A radionuclide generator (an option?)

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Principles of a Generator

- In a generator:
  - A long-lived parent nuclide is allowed to decay to its short-lived daughter nuclide, and
  - The latter is then chemically separated.
- The generator is easily transportable and serve as sources of short-lived radionuclides.

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- An ideal radionuclide generator should be:
  - Simple
  - Convenient
  - Rapid to use
  - Give a high yield of the daughter nuclide repeatedly and reproducibly
  - **Properly shielded to minimize radiation exposure**
  - Strong and compact for shipping

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- Generator systems important in nuclear medicine:
  - **^{99}Mo – ^{99m}Tc**
  - ^{113}Sn – ^{113m}In
  - ^{82}Sr – ^{82}Rb
  - ^{68}Ge – ^{68}Ga

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^{99}Mo – ^{99m}Tc Generator system

- ^{99}Mo (parent, $t_{1/2}$ of 66 hrs) and decay to the metastable state ^{99m}Tc
- ^{99m}Tc (daughter, $t_{1/2}$ of 6 hrs) and decays to ^{99}Tc (stable one) by isomeric transition of 140 keV (***emit gamma ray***)
  - Ideal for imaging devices in nuclear medicine.

Ideal properties of radiopharmaceutical

1) Easy Availability

- Should be easily produced, inexpensive, and readily available in any nuclear medicine facility.

2) Short Effective Half-Life

- Physical half-life (Tp)
- Biologic half-life (Tb)

Effective half-life (Te) can be calculate

Ideal properties...

- In any biologic system, the loss of a radiopharmaceutical is due to both the **physical decay** of the radionuclide and the **biologic elimination** of the radiopharmaceutical
- Therefore the effective half-life can be given as:

$$\frac{1}{T_e} = \frac{1}{T_p} + \frac{1}{T_b} \qquad T_e = \frac{T_p \times T_b}{T_p + T_b}$$

- Radiopharmaceuticals should have a relatively short effective half-life, which should not be longer than the time necessary to complete the study in question.

Ideal properties...

Example

- The physical half-life of ^{111}In is 67 hr and the biologic half-life of ^{111}In-DTPA used for measurement of the glomerular filtration rate is 1.5 hr. What is the effective half-life of ^{111}In-DTPA?

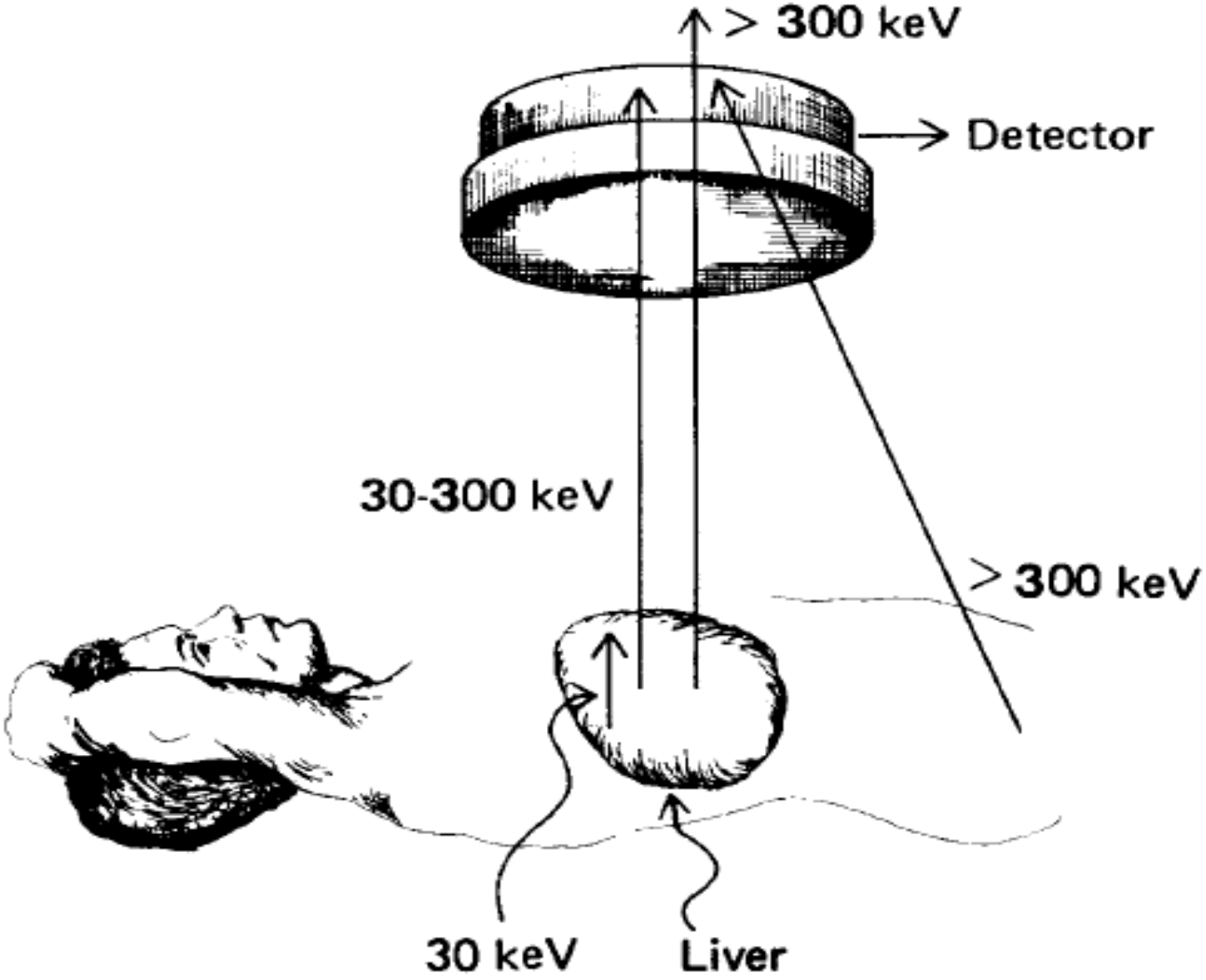
$$T_e = \frac{1.5 \times 67}{67 + 1.5} = \frac{100.5}{68.5} = 1.47 \text{ hr}$$

3) Appropriate radiation

- Particle Emission (α- and β)
  - Should not be used as the label in *diagnostic* radiopharmaceuticals.
  - Useful for therapy, because of the effective radiation *damage* to *abnormal* cells.
- Gamma (γ) emitter
  - For diagnostic studies,
  - Radiation energy preferably between 30 & 300 keV

Ideal properties...

- Gamma (γ)emitter
  - For diagnostic studies the radionuclide must emit a γ radiation with an energy preferably between 30 and 300 keV.
    - Below 30 keV, γ rays are absorbed by tissue and are not detected by the detector
    - However, too high an energy will result in the gamma ray penetrating the detector of the imaging device without being stopped and hence recorded.


> 300 keV
Detector
30-300 keV
> 300 keV
30 keV
Liver

4) High Target-to-Non-target activity ratio

5) Low dose rate to both patient and personnel

6) Non-toxicity of radiopharmaceuticals

7) Chemical Reactivity

- Should react with variety of substrates for radiolabeling reactions

8) Chemical stability during use

9) Ease of preparation and appropriate QC

- Several steps and a complex variety of equipment should not be required.
- Quality control procedures should be available to check each batch of the radiopharmaceutical reconstituted in the working laboratory.

Ideal properties…

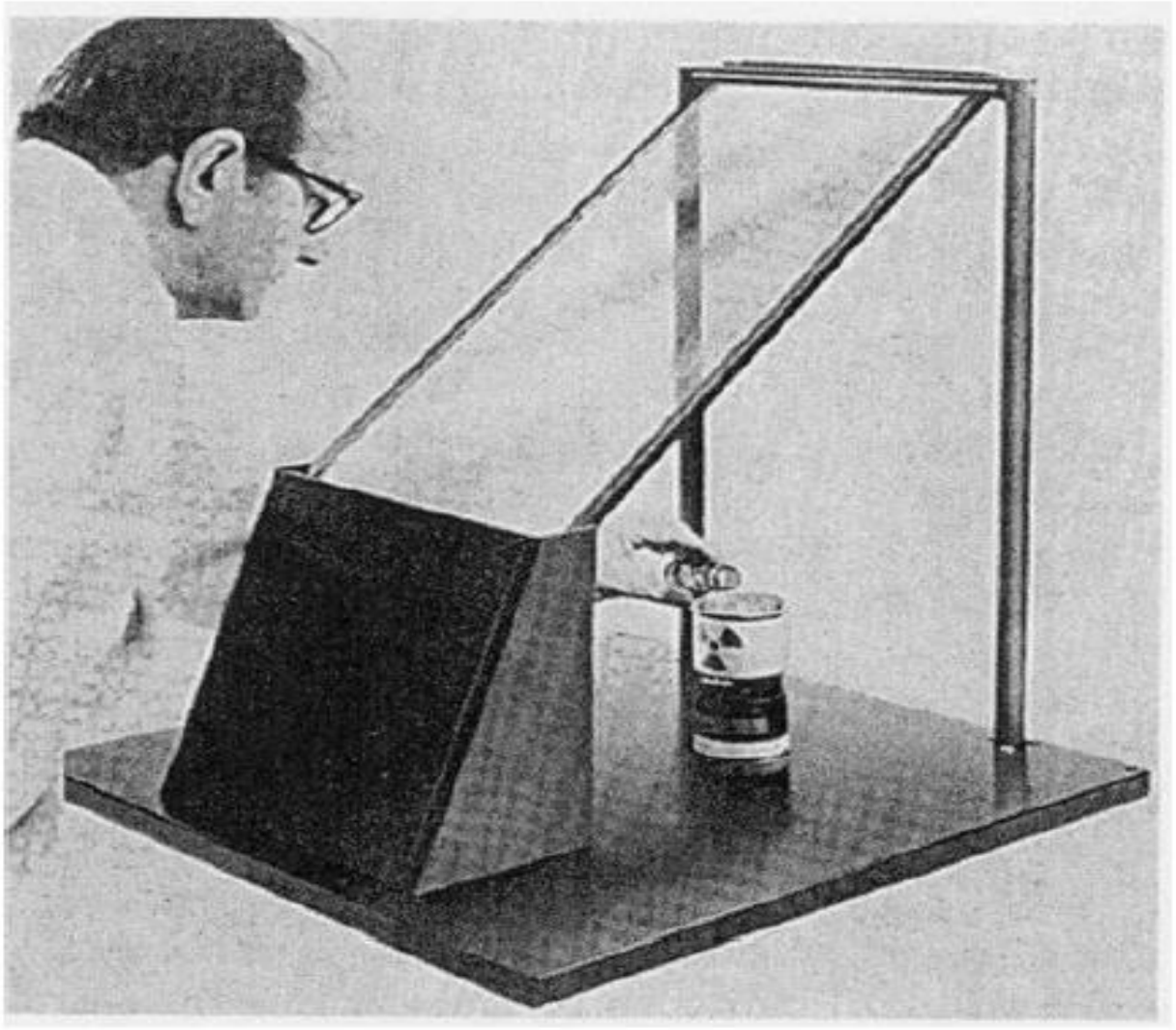
It is difficult for a given radiopharmaceutical to meet all these criteria and the one of choice is the best of many compromises.

Storage of radiopharmaceuticals

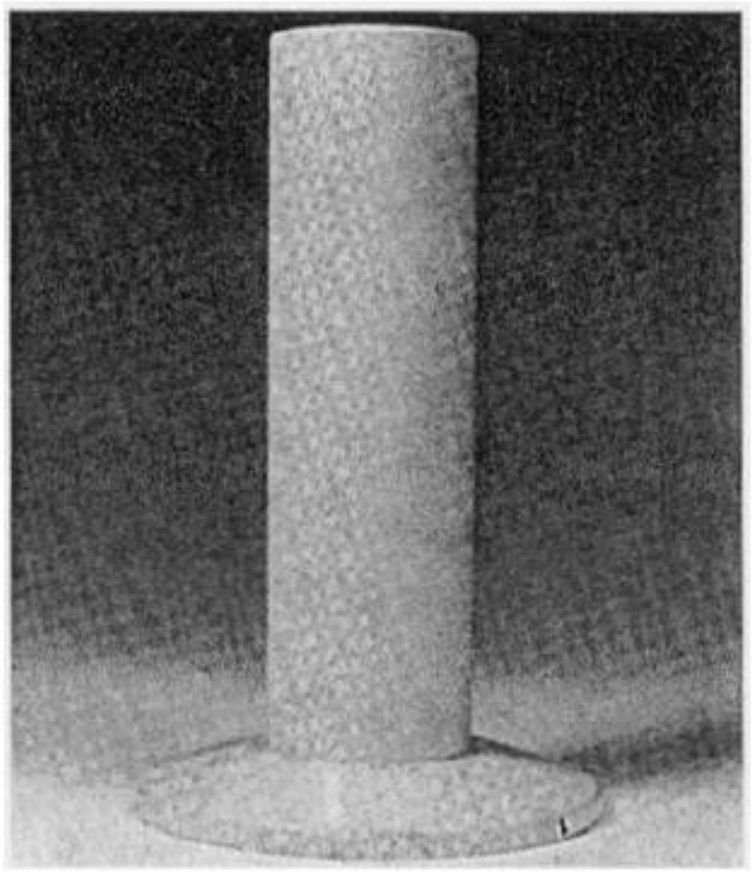
- Should be properly stored so that they are not degraded by light or temperature.
- Since radiation exposure is a serious problem in the nuclear pharmacy, the vials or syringes containing radiopharmaceuticals must be stored in a shielded area.
- Various high atomic number materials that absorb radiations can be used to provide radiation protection.

Storage…

- Since the ranges of α and β particles are short in matter, the containers themselves act as shields for these radiations.
- γ radiations are highly penetrating, and therefore highly absorbing material must be used for shielding.
  - For economic reasons, lead is most commonly used for this purpose.



Lead barrier shield, behind which all formulations and manipulations of radioactive materials are carried out.



Lead-shield syringe holder for transporting the syringes containing radioactive material.

Radioactive Waste Disposal

- Radioactive wastes (e.g., syringes, needles, vials, liquid waste, gas, and contaminated papers, tissues, and liners) are disposed either by:

  a) *Decay-in-storage (radionuclides with* $t_{1/2} < 120$ days)

  b) *Release into a sewerage system (radionuclides soluble in water)*

  c) *Transfer to authorized recipient (long-lived radionuclides)*

  d) *Other methods: e.g., incineration and atmospheric release of radioactive gases*

Radioactive Waste Disposal

Decay-in-storage

- Radionuclides with half-lives less than 120 days usually are disposed of by this method.
- **The waste is allowed to decay for a period of time** and then surveyed. If the radioactivity of the waste cannot be distinguished from background, it can be disposed of in the normal trash after removal of all radiation labels.
- This method is **most appropriate for short-lived radionuclides** such as ^{99m}Tc, ^{123}I, ^{201}Tl, ^{111}In, and ^{67}Ga, and therefore it is routinely employed in nuclear medicine.

Radioactive Waste Disposal

- Radioactive waste should be stored separately according to the similar half-lives of radionuclides for convenience of timely disposal of each radionuclide.

Release into a Sewerage System

- Radioactive waste disposal into a sewerage system is permitted provided the radioactive material is soluble (or dispersible biological material) in water.
- Disposal depends on the flow rate of water but is limited to 1 Ci (37 GBq) of ^{14}C, 5 Ci (185 GBq) of ^{3}H, and 1 Ci (37 GBq) for all other radionuclides annually.

Radioactive Waste Disposal

Transfer to an Authorized Recipient

- A transfer to an authorized recipient method is adopted for ***long-lived radionuclides***
- Usually involves transfer of radioactive waste to authorized commercial firms that bury or incinerate at approved sites or facilities.

Radioactive Waste Disposal

Other Disposal Methods

- Radioactive waste disposal methods other than those mentioned above may be adopted, provided approval is obtained from the regulatory agency.
- The impact of such disposal methods on the environment, nearby facilities, and the population is heavily weighed before approval is granted.
- Examples
  - ***Incineration of carcasses of research animals containing radioactive materials***